Optimizing Immunosuppression With Sirolimus in the First Year Posttransplantation: Experience in the United States

M.R. Weir and R.K. Wali

ABSTRACT

Early and late kidney graft survival has improved considerably due to advances in clinical care, particularly immunosuppression. Many of the kidney transplants functioning today should serve their new owners for their life expectancy. What challenges this viewpoint and the main cause of late kidney function deterioration remains allograft nephropathy. Often this reflects an influence of the immunosuppression. Subclinical rejection, chronic nephrotoxicity, recurrent disease, infections, or diabetes may also contribute to this process. Optimal early and late immunosuppression is required, which provides efficacy without attendent risk for graft dysfunction due to nephrotoxicity. Since 1-year serum creatinine level often provides an indication of long-term graft function, early evaluation of subtle degrees of graft dysfunction should prompt a graft biopsy to identify treatable causes.

THE mammalian target of rapamycin (mTOR) inhibitors have been available for clinical use in the United States for approximately 10 years.[1] As with all immunosuppression medications, there is a learning curve to develop strategies for optimal use. Currently, the mTOR inhibitor, sirolimus, is approved for de novo use with cyclosporine as part of a multi-drug immunosuppression regimen. However, some centers prefer not to use sirolimus for de novo immunosuppression, particularly in obese patients, because of problems with wound healing.[2] Others have noted that the mTOR inhibitors may prolong delayed graft function,[3] which is another concern with de novo use of sirolimus unless patients have immediate graft function. On the other hand, there may be an important opportunity for planned early conversion from calcineurin inhibitors (CNI) to mTOR inhibitors in stable patients during the first 6 months posttransplantation as a means of improving graft function.[4]

It is remarkable that, with the improvements in immunosuppression medications and the reduction in acute rejection rates, there has been only minimal improvements in graft survival.[5] The purpose of this brief report will be to describe our clinical experience at the University of Maryland Medical Center with CNI-sparing approaches, as well as our participation in a multi-center clinical trial to evaluate optimal timing for a CNI to mTOR inhibitor conversion during the first 6 months posttransplantation with a background of mycophenolate mofetil (MMF) immunosuppression.

LEADING CAUSES OF GRAFT FAILURE

The major causes of kidney graft failure are allograft nephropathy and cardiovascular disease (also known as death with functioning graft). One has to wonder whether or not these processes may be related, given the fact that vascular disease in the native circulation and in the transplant kidney can be affected by inflammation, hypertension, diabetes, and dyslipidemia. Cardiovascular disease is much more common among renal transplant recipients compared with the general population.[6] The greater incidence of cardiovascular disease is not entirely explained by traditional risk factors, such as hypertension, dyslipidemia, and diabetes. Consequently, other factors may be involved, such as immunosuppression, alloimmune responses, and infection. Kasiske et al described the observed and the expected risk for ischemic heart disease after kidney transplantation, and noted that the 10-year survival without ischemic heart disease was markedly reduced in kidney transplant recipients, particularly if they were diabetic, older, and smokers.[6]

From the Division of Nephrology, Department of Medicine, University of Maryland School of Medicine, Baltimore, Maryland, U.S.A.

Dr Wali has received grant support from Wyeth and has served on the Wyeth speakers bureau.

Address reprint requests to Matthew R. Weir, MD, Division of Nephrology, University of Maryland School of Medicine, 22 South Greene Street, Room N3W143, Baltimore, MD 21202. E-mail: mweir@medicine.umaryland.edu

© 2009 by Elsevier Inc. All rights reserved.
360 Park Avenue South, New York, NY 10010-1710

0041-1345/09/$–see front matter
doi:10.1016/j.transproceed.2009.06.096

Consequently, more focus on the increased risk for cardiovascular disease is needed in the kidney transplant recipient.

IMPORTANT PREDICTIVE VALUE OF KIDNEY FUNCTION AT 1 YEAR

It has also been noted that decreased renal function is a strong predictive factor for cardiovascular death following renal transplantation.[5] Meier-Kriesche et al used the United States Renal Data System (USRDS) registry to evaluate the information on more than 48,000 first transplant recipients who were followed between the years of 1988 and 1998.[7] Multi-organ transplants were excluded, and only adults were analyzed. All patients who had a functioning graft at 1 year posttransplantation, defined as those having a serum creatinine level <4 mg/dL, were included. As one can see in Fig 1, cardiovascular death was continuously related to serum creatinine levels >1.3 mg/dL. Thus, there is an independent association between decreased renal function and an increased risk for cardiovascular death. The degree of renal dysfunction strongly correlates with the risk of cardiovascular death.

One-year renal function in kidney transplant recipients is also a candidate as a surrogate marker of graft loss.[8] Between the years 1988 and 1994, both acute rejection rates and graft survival rates steadily improved. As one can see in Fig 2, graft survival, although improved, still appears to have the same slope of decay of graft survival for each level of kidney function over a period of 5 years.[9] One has to wonder whether or not it is an improved intercept (higher baseline glomerular filtration rate [GFR]) that is accounting for improved graft survival. Improvement of slope of loss of kidney function does not appear as important. It is these concepts that are most important in evaluating future strategies for prolonging graft function. Ideally, each kidney should serve their owner for their remaining life expectancy. Thus, one has to consider the intercept and slope, or both, as possible targets of therapeutic intervention and improvement. If baseline GFR is improved with the same slope of decay of function over time, then duration of graft function would improve. On the other hand, if the slope of decay of kidney function were improved, then the intercept (ie, baseline kidney function) may not be quite as important in prolonging graft function.

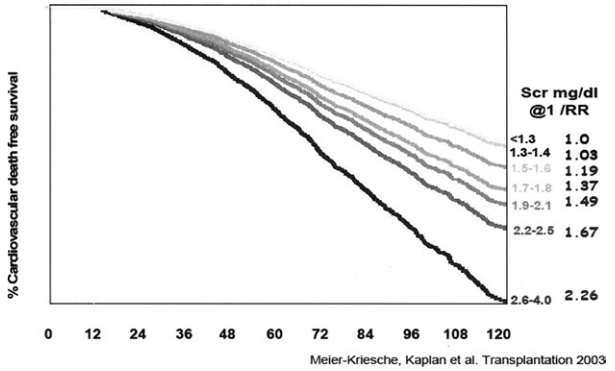

Fig 1. Cardiovascular death events in 48,832 kidney transplant recipients based on serum creatinine levels (mg/dL) at 1 year posttransplantation. Reproduced with permission from Meier-Kriesche H-U, et al. Transplantation. 2003;75:1291–1295.

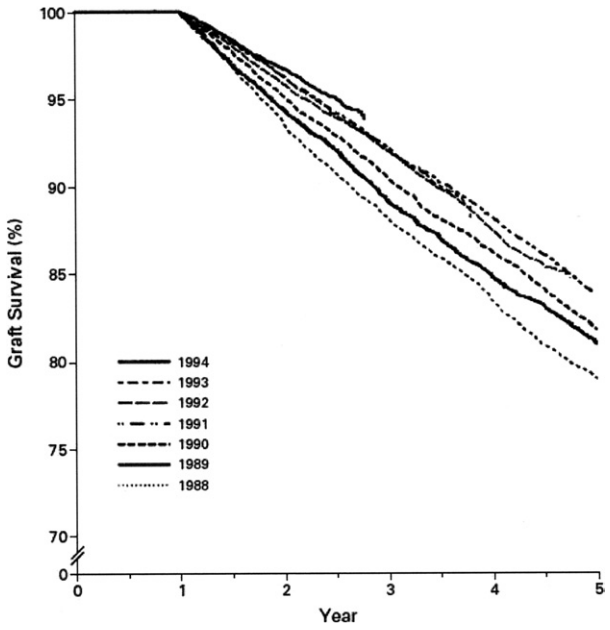

Fig 2. Functional cadaveric graft survival (censored for death with functioning graft) after the first year posttransplantation. Copyright © 2000 Massachusetts Medical Society. All rights reserved.

OLDER VERSUS NEWER ASSUMPTIONS ABOUT KIDNEY GRAFT FUNCTION

Traditional assumptions have been that early kidney function predicts late kidney function. That is, those patients with higher serum creatinine levels were more likely to have progressive deterioration of function. Another assumption is that graft loss is inevitable for every kidney transplant recipient because most patients have negative slopes. However, these traditional assumptions are not supported by recent data.[10] Perhaps even more important is that kidney function can improve during the first year posttransplantation and many patients with impaired kidney function demonstrate prolonged graft function.[11,12] Thus, it is better not to generalize, and more important to individualize considerations about how best to protect kidney function in each transplant recipient.

One has to consider that there are 2 practical areas of immunosuppression strategy. The first area is in the early posttransplant period. During this time period it is important to provide sufficient immunosuppression to avoid rejection and yet not global immunodepression. After the first 3–6 months, the priority should change to consider long-term immunosuppression strategies that are devoid of risk to both the patient and the graft. Key considerations

Download English Version:

https://daneshyari.com/en/article/4261391

Download Persian Version:

https://daneshyari.com/article/4261391

Daneshyari.com